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TITLE PAGE

Title: The effect of vasoactive drugs on mortality in patients with severe sepsis and septic shock. A network meta-analysis of randomized trials

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ABSTRACT

Purpose: Inotropes and vasopressors are cornerstone of therapy of septic shock, but search for the best agent is ongoing. We aimed to determine which vasoactive drug is associated with improved survival.

Materials and Methods: PubMed, BioMedCentral, Embase and the Cochrane Central Register were searched. Randomized trials performed in the setting of sepsis with at least one group allocated to inotrope/vasopressor were included. Network meta-analysis with a frequentist approach was performed.

Results: The 33 included studies randomized 3,470 patients to 16 different comparators. As compared with placebo, levosimendan (Odds Ratio [OR] = 0.17, 95% Confidence Interval [CI] = 0.05 – 0.60), dobutamine (OR = 0.30, 95% CI = 0.09 – 0.99), epinephrine (OR = 0.35, 95% CI = 0.13 – 0.96), vasopressin (OR = 0.37, 95% CI = 0.16 – 0.89), and norepinephrine plus dobutamine (OR = 0.42, 95% CI = 0.11 – 0.96) were significantly associated with survival. Norepinephrine improved survival compared with dopamine (OR = 0.81, 95% CI = 0.66 – 1.00). Rank analysis showed that levosimendan had the highest probability of being the best treatment.

Conclusions: Among several regimens for pharmacological cardiovascular support in septic patients, regimens based on inodilators have the highest probability of improve survival.

KEY WORDS

Sepsis, vasopressors, inotropes, intensive care, microcirculation, mortality

INTRODUCTION

Severe sepsis is widely recognized as a major health issue. It occurs in up to one-third of patients admitted to an intensive care unit (ICU) [1], and has an estimated incidence of up to 19 million in the world [2] with a raising incidence [3, 4]. Although mortality rate in developed countries has decreased in recent years, it remains as high as 20 to 30% [1, 3, 5], and may reach 40% when septic shock develops [3].

Early hemodynamic stabilization is considered a critical issue in the management of septic patients. International guidelines recommend administration of intravenous fluids and, when volume replacement is not sufficient to restore adequate tissue perfusion, administration of vasoactive agents [6]. Norepinephrine and dobutamine are currently the recommended first-line vasoactive drugs [6]; however, use of other agents such as dopamine, epinephrine, phenylephrine, vasopressin or terlipressin has also been investigated and the search for the best agent is still ongoing [7-11]. Each drug has different pharmacological effects, with a unique theoretical profile of advantages and disadvantages [12]. Notably, in recent years, inodilators have also been frequently tested in septic shock patients with the aim to improve cardiac function, which is often compromised in severe sepsis even in patients with no previous cardiac disease [13]. Inodilators may correct several cardiac and hemodynamic alterations associated with septic shock [13]. However, their vasodilating effect may also impair tissue perfusion by excessively lowering mean arterial pressure (MAP).

Although several randomized trials comparing one agent with one of the others exists, most are small and, furthermore, do not allow for an indirect comparison between the different agents [14]. A network meta-analysis is a statistical technique that allows an indirect comparison between treatments that has never been investigated one against the other in randomized clinical trials [15, 16]. There are currently no meta-analyses which compare vasoactive drugs in septic shock including also inodilators. Therefore, we performed a network meta-analysis to indirectly compare and grade all the vasoactive drugs ever tested in randomized controlled trials (RCTs) in septic patients in order to identify the treatment associated with the highest survival rate.

MATERIAL AND METHODS

This work was designed as a systematic review and network meta-analysis, with reporting following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [17-20] (PRISMA-NMA Checklist available as Supplementary Material). Endpoint of our study was mortality at the longest follow-up available.

Data Sources and Searches

Firstly, two investigators independently searched relevant studies on PubMed, Embase, BioMed Central and the Cochrane Central register. Our aim was to find all RCTs in which an inotrope or a vasopressor, regardless of the molecule type, was tested against any type of control (including other drugs, placebo, or standard treatment without placebo) performed in the setting of sepsis. We accordingly developed a search strategy. In addition, when other meta-analyses, systematic reviews, or large RCTs were found, we employed backward snowballing (i.e., scanning of references of retrieved articles and pertinent reviews) to obtain further studies. Literature search was last updated June 30th, 2015 and the full PubMed search strategy, modified from Biondi-Zoccai et al [21], is available in the Supplementary Material.

Study Selection

Investigators first examined references at a title/abstract level, with divergences resolved by consensus, and then, if potentially pertinent, retrieved the complete articles. Articles were included in the meta-analysis if they fulfilled the following inclusion criteria: random allocation to treatment, at least one group randomized to receive an inotrope or a vasopressor agent, patients with sepsis. We applied no restriction in the type of control treatment (e.g. other vasoactive agents, placebo, or standard treatment), severity of sepsis (sepsis, severe sepsis or septic shock), or setting of treatment. We excluded trials performed in setting other than sepsis, investigating non-adult population,

studies on overlapping population (i.e. secondary analyses of a previously published trial), studies not reporting mortality data, study published as abstract only, and animal studies. We also decided to exclude studies investigating drugs currently not available on the market neither in Europe nor in the United States.

Data Extraction and Quality Assessment

Baseline, procedural, outcome and follow-up data were independently abstracted by two investigators. Patients randomized to placebo and standard treatment were aggregated together as a single comparison group. In cases of trials randomizing patients with different types of shock [7, 8], only data from patients with septic shock were abstracted. Data were analysed according to the intention-to-treat principle whenever possible. The internal validity and risk of bias of included trials was appraised by two independent investigators according to the "Risk of bias assessment tool" developed by The Cochrane collaboration [22]. Briefly, for each trial seven domains were assessed: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data reporting, selective reporting, and presence of other bias. Presence of possible source of bias in each domain was assessed, and a final judgement of low, moderate or high risk of bias was assigned.

Data Synthesis and Analysis

Dichotomous variables were reported as percentages while continuous variables were reported as mean ± standard deviation or median (interquartile range). Network meta-analysis with a frequentist approach was used to compare mortality at the longest follow-up available between different therapies using the netmeta R package version 8.0 (Available at: http://CRAN.R-project.org/package=netmeta) to calculate point estimates of odds ratios (OR) with 95% confidence intervals (CI) and generate head to head comparison and forest plots using random-effects models comparing the effect estimates of different therapies relative to placebo [23]. P rank scores were

generated to determine probability scores to rank which therapies result in the lowest in-hospital mortality. Heterogeneity and inconsistency were assessed and heat plots were also generated which is a matrix visualization proposed by Krahn and colleagues [24] that highlights hot spots of inconsistency between specific direct evidence in the whole network and renders transparent possible drivers. In addition, small study effects were appraised by visual inspection of adjusted funnel plots. Once results of the network meta-analysis were obtained, we also performed an unplanned, traditional meta-analysis to compare the effect of levosimendan versus dobutamine on mortality. Details on the analysis methods for the traditional meta-analysis are provided in the Supplementary Material. Statistical analysis was performed using Stata 13 (StataCorp, College Station, TX, USA), R [25] and RevMan (Review Manager version 5.3, The Nordic Cochrane Center, The Cochrane Collaboration, Copenaghen, 2014), with statistical significance for hypothesis testing set at the 0.05 two-tailed level and for heterogeneity testing at the 0.10 two-tailed level.

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RESULTS

Study characteristics

A total of 467 studies were identified through database search, and a total of 61 articles were retrieved as complete article. Of these, 28 studies were excluded due to pre-specified criteria (a list of excludied studies, together with reason for exclusion, is presented in Supplementary Table 1 in Supplementary Material), and a total of 33 studies randomizing 3,470 patients in 16 treatment groups was included in the final analysis (Figure 1, Table 1, Supplementary Table 2 in Supplementary Material) [7-11, 26-53]. Three studies randomized patients to three groups [10, 46,

49], while all the others compared only two groups. Five studies were multicenter trials [7-9, 27, 34].

The most frequently investigated comparators were norepinephrine (1,218 patients – 13 studies) (7-11, 26, 31, 34, 39-41, 47, 48), dopamine (1,141 patients – 8 studies) [7, 30, 39-41, 47-49], vasopressin (424 patients – 5 studies) (9, 10, 34, 36, 38), epinephrine (302 patients – 6 studies) [8, 27, 35, 37, 49, 50], combination of norepinephrine plus dobutamine (195 patients – 3 studies) [27, 35, 50], and dobutamine (129 patients – 6 studies) [28, 32, 37, 42, 44, 45].

Longest follow up was variable among different studies. The most frequently reported follow-up were ICU stay in 14 studies [10, 11, 29, 31, 32, 34, 36, 39, 41, 42, 46, 48, 50], 28 or 30 days in further 14 studies [7-9, 27, 28, 30, 33, 37, 44, 47, 49, 51, 52, 53], and 90 days in 5 studies [9, 10, 27, 51, 52].

Trials were on average of moderate quality, with a total of 10 studies judged to carry a low risk of bias, 21 a moderate risk of bias, and 2 a high risk of bias (Supplementary Material). This limitation should be viewed in light of the reliance on all-cause mortality, which is less prone to adjudication and attrition bias.

Quantitative Data Synthesis

Overall sixteen active treatments along with placebo were tested in 33 RCTs identified (Figure 1, Table 1). A total of 39 pairwise comparisons were finally available. Head to head comparison obtained by network meta-analysis is shown in Table 2. Overall, only five out of 16 active treatments investigated were effective in reducing mortality when compared to placebo (Supplementary Figure 1 in Supplementary Material) including epinephrine (OR for epinephrine versus [vs] placebo = 0.35, 95% CI = 0.13 to 0.96), vasopressin (OR for vasopressin vs placebo = 0.37, 95% CI = 0.16 to 0.89), dobutamine (OR for dobutamine vs placebo = 0.30, 95% CI = 0.09 to 0.99), levosimendan (OR for levosimendan vs placebo = 0.17, 95% CI = 0.05 to 0.60) and the combination between norepinephrine and dobutamine (OR for norepinephrine + dobutamine vs

placebo = 0.42, 95% CI = 0.11 to 0.96). Of note, dopamine was associated with significantly increased mortality when compared to other agents such as norepinephrine (OR for dopamine vs norepinephrine = 1.23, 95% CI 1.00 to 1.52) vasopressin (OR for dopamine vs vasopressin = 1.56, 95% CI 1.11 to 2.19) and levosimendan (OR for dopamine vs levosimendan = 3.67, 95% CI 1.04 to 10.97).

Rank analysis showed that among treatments found to be significantly associated with reduced mortality, levosimendan showed the highest probability to be the best (85%) when compared to dobutamine (65%), combination of norepinephrine plus dobutamine (64%), epinephrine (60%) and vasopressin (59%) (Supplementary Figure 2 in Supplementary Material).

Results of a traditional meta-analysis comparing levosimendan versus dobutamine showed no difference between the two agents in terms of mortality (risk ratio for levosimendan versus dobutamine = 0.78, 95% CI 0.56 to 1.09, I^2 = 0%, with four studies included [28, 42, 44, 45]) (Supplementary Figure 3 in Supplementary Material).

There was no significant heterogeneity/inconsistency among comparisons investigated (I^2 = 0%; Q statistics P value whole network P = 0.99; within designs P = 0.99; between designs P = 0.94). Heat plot showed only mild inconsistency only among terlipressin vs vasopressin vs norepinephrine comparison.

Finally, inspection of comparison-adjusted funnel plot did not disclose significant small study effects or publication bias (Supplementary Figure 4 in Supplementary Material).

DISCUSSION

To the best of our knowledge, this is the largest meta-analysis ever performed on vasoactive drugs in septic patients. Furthermore, we compared for the first time therapeutic regimens including inodilators drug with regimens including inconstrictors or pure vasoconstrictors. The most important finding of our study is that, among 16 different treatments or combination of treatments, inodilators such as levosimendan and dobutamine showed the highest probability of being the

agents associated with the lowest mortality. These results are particularly interesting as our traditional view of hemodynamic management of septic shock has been recently challenged by several large RCTs [70-72], while our understanding of the complex pathophysiology of septic cardiovascular dysfunction is increasing [13, Guarracino 2014 Crit Care].

Hypotension is almost universally present in septic shock [54], and administration of drugs with the potential of further lowering mean arterial pressure (MAP) may seem counterintuitive in this setting. The findings of our meta-analysis can be explained hypothesizing that coadministration of inodilators and vasoconstrictors improves microcirculatory perfusion. In recent years, the role of microcirculatory dysfunction in circulatory shock has been increasingly recognized [55, 56], and there is growing evidence that sufficient cardiac output (CO), MAP and calculated systemic oxygen delivery may not imply adequate tissue perfusion [57, 58]. Inodilators have microcirculatory effect independent from those on macrocirculation [59, 60]. Furthermore, conventional hemodynamic resuscitation may not correct microcirculatory alterations [61]. On the contrary, excessive vasopressor administration and subsequent vasoconstriction could have a detrimental effect on the overall oxygen consumption/delivery balance [62]. With the combination of both cardiac output augmentation and peripheral vasodilation, inodilatory agents might be able to improve tissue oxygenation, which is the ultimate determinant of organ function, to a better extent than inoconstrictors alone.

Beneficial effects of inodilators on microcirculation have been documented also in settings other than septic shock. Den Uil and colleagues investigated the effect of enoximone, dobutamine, and norepinephrine on microcirculatory function in patients with acute myocardial infarction and cardiogenic shock [61]. They found that enoximone has the most favourable effect on microcirculation, and patients with improved microcirculatory function have a higher probability of survival [61]. Pirracchio and colleagues also investigated the effect of adding an inodilators to inoconstrictors in patients with cardiogenic shock, and their study suggested that inodilator administration may improve short-term mortality [62]. However, hemodynamic characteristics of

septic and cardiogenic shock are different [53], and this may limit the generalization of these results also to septic shock patients.

Among the different agents, we found that levosimendan has the highest probability of being the best. This might be explained by the different mechanism of action and side effects profile of levosimendan as compared with dobutamine and other catecholamines [64-66]. All catecholamines increase myocardial oxygen consumption, increase heart rate, and can trigger arrhythmias. Furthermore, excessive adrenergic stimulation is associated to additional metabolic and immunological side effects [66], and excessive levels of catecholamines are thought to be involved in the pathophysiology of septic cardiomyopathy [13, Coppola 2015 Crit Care]. Compared with catecholamines, levosimendan does not stimulate adrenergic receptors, causes little increase in myocardial oxygen consumption and may on the contrary have a cardioprotective effect [64-65]. Furthermore, levosimendan improves diastolic function (a key element of septic cardiomyopathy [13]) to a better extent than dobutamine [Dominguez-Rodriguez 2008 Int J Cardiol] and improves ventriculo-arterial coupling [Guarracino 2007 Acta Anaesthesiol Scand, Guarracino 2014 Crit Care], another recently described aspect of impairment of left ventricular function due to sepsis [13, Guarracino 2014 Crit Care] . [44, 45]. Of note, we found no difference in mortality when comparing levosimendan and dobutamine both using a network approach and a traditional meta-analysis, as already suggested by previous studies [Zangrillo 2015 J Crit Care]. Nevertheless, we observed a small trend towards mortality reduction in the levosimendan group. Interestingly, while levosimendan underwent an extensive investigation in several RCTs [Belletti 2015 Br J Anaesth], no RCTs on dobutamine use in patients with sepsis has been published, although dobutamine is recommended an inotrope of choice by the Surviving Sepsis Campaign guidelines [6], while levosimendan is not event mentioned. Hopefully, the ongoing Levosimendan for the Prevention of Acute oRgan Dysfunction in Sepsis (LeoPARDS - ISRCTN12776039) multicenter RCT will answer the question of whether levosimendan administration improve organ function in patients with sepsis [67].

Another important RCT which is going to provide further insights on the best hemodynamic treatment of septic shock is the VAsopressin versus Noradrenaline as Initial therapy in Septic sHock (VANISH - ISRCTN20769191) trial, which investigated the effect of early administration vasopressin and hydrocortisone using a 2x2 factorial design [Gordon 2014 BMJ Open]. Results of this study are strongly awaited, as in previous meta-analyses [Serpa Neto 2012 Crit Care, Belletti 2015 PLoS One] and also in our study has been suggested that early vasopressin administration might improve survival in septic patients [Russell 2009 Crit Care Med].

As of today, supportive treatment for septic shock focused on administration of fluids and vasopressors in the first place, with the goal of maintaining an adequate MAP, with addition of inotropes and/or blood products if a sufficient tissue perfusion can not be obtained, or if evidences of cardiac dysfunction exists [6]. Dobutamine is currently the only inotrope recommended by guidelines, although with a low grade of evidence, while norepinephrine is suggested as first-line vasoconstrictor [6]. Since the landmark trial from Rivers et al. [68], hemodynamic management of septic shock focused on parameters reflecting macrocirculatory function, i.e. MAP, central venous pressure (CVP), and central venous oxygen saturation ($ScvO_2$) [6, 69]. However, several large, multicenter RCTs have recently challenged this traditional approach [70-72]. While early diagnosis of sepsis and prompt antibiotic administration have been recognized to clearly improve outcome and have now entered routine clinical practice, the optimal approach to hemodynamic monitoring and management remains controversial. In every day clinical practice, MAP is often considered the most important hemodynamic parameters in patients with shock, as MAP lower than 60-65 mmHg is associated with a poor outcome [57]. On the other side, it has been demonstrated that CVP is a poor index of volume status [73], and excessive fluid administration is detrimental [74]. Implementation of resuscitation-protocols based on dynamic indices of fluid responsiveness could help to overcome these issues and allow a patient-targeted fluid administration [69]. In addition, devices capable of directly monitoring microcirculation and tissue oxygenation are now available [75], and their use might further improve development of patient-specific treatment algorithms.

Oba and Lone published a Bayesian network meta-analysis investigating the effect of inotropic and vasopressors agents in septic shock which included 14 studies randomizing a total 2811 patients [76]. They concluded that norepinephrine and the combination of norepinephrine plus low-dose vasopressin might improve survival as compared with dopamine alone. On the contrary, they found that addition of an inotropic agent to treatment did not reduce mortality.

Zhou et al. recently published a network meta-analysis of 21 studies (3819 patients) investigating the effect of vasopressors in patients with septic shock [77]. They concluded that norepinephrine may be superior to dopamine as a vasopressor in septic shock in terms of patients' survival [77]. Compared with these two meta-analyses, we included a larger number of studies investigating a wider range of vasoactive agents. Furthermore, two of the studies [78, 79] included by Zhou et al. were actually sub-studies of a larger multicenter RCT [9], artificially increasing the overall number of patients by 1019. Our results differ from those of previous meta-analyses because we included in our analysis a larger number of studies, investigating also inodilatory agents. While we also found that norepinephrine may be superior to dopamine, as already suggested by other works [80, 81], our most important finding is that addition of inodilators agents seems to be superior to treatment with vasopressors alone. Interestingly, in our study norepinephrine was not associated to increased survival as compared with placebo/standard treatment. This should not surprise, as all patients randomized to "control" group also received the best available treatment, which include norepinephrine or other vasoconstrictors (Supplementary Table 2).

Our study has some limitations. First of all, despite the large number of trials and patients included, the majority of the studies were small, single-center trials, which poses them at high risk for biases [82, 83]. Another important limitation is the inclusion of a large number of treatments (16 treatments). Furthermore, we acknowledge that few of included trials were relatively old, and were published before the landmark trial of Rivers et al [68] that had a strong impact on management of septic shock. However, we preferred to include these trials, as other Authors did [76, 77, 80, 81], in order to provide the most complete analysis possible with current evidence. Furthermore, the same

limitations of traditional meta-analyses also apply to network meta-analyses [16-18]. In particular, meta-analyses should be viewed as hypothesis-generating tools, rather than providing definitive evidences. Therefore, our results, although providing interesting insights on management of septic shock, should be confirmed with adequately designed and adequately powered multicenter randomized trials. Notably, hemodynamic management of septic shock is a complex issue involving not only vasoactive drugs but also fluids, and timing of intervention is also critical [84]. Future studies should focus on finding the best combination of fluids, vasopressors and inotropes to achieve sufficient tissue perfusion, rather than normal "gross" hemodynamic parameters, and we will likely move towards individualized rather than protocolized hemodynamic management [57, 85]. In addition, both short- and long-term follow-up should be reported [86].

CONCLUSIONS

In patients with septic shock, use of inodilators is associated with the highest survival probability. Among 16 different treatment regimens, levosimendan is the most promising, followed by dobutamine and a combination of dobutamine plus norepinephrine. Nevertheless, available evidence is still insufficient to recommend such treatment because of lack of high-quality, multicenter RCTs. Future RCTs focusing on the role of inodilators in septic shock are warranted.

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CONFLICT OF INTEREST

Dr. Landoni received speaker fees from AbbVie, Orion and Tenax.

Dr. Biondi-Zoccai has consulted or lectured for Bayer and Novartis.

The remaining Authors have disclosed that they do not have any conflict of interest.

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FIGURE CAPTIONS

Figure 1. Flow-diagram of selection of articles.

Figure 2. Network configuration. Amr: amrinone; Dbt: dobutamine; Dop: dopamine; Dpx: dopexamine; Enx: enoximone; Epi: epinephrine; Lvs: levosimendan; MtB: methylene blue; Nor: norepinephrine; Phe: phenylephrine; Plac: placebo/standard treatment; Ter: terlipressin; Vas: vasopressin.